44. (Amended) A method for suppressing growth of a tumor cell that expresses an APRIL ligand polypeptide, comprising the step of exposing said cell to an effective amount of an antibody directed to said APRIL ligand polypeptide capable of interfering with an interaction between said APRIL ligand polypeptide and an APRIL receptor.

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45. (Amended) A method for suppressing growth of a tumor cell that expresses an APRIL receptor polypeptide, comprising the step of exposing said cell to an effective amount of an antibody directed to an APRIL ligand polypeptide capable of interfering with an interaction between said APRIL ligand polypeptide and said APRIL receptor polypeptide.

REMARKS

Applicant acknowledges with appreciation the Examiner's withdrawal of the rejection under part (A) of pages 4-5 of the July 9, 2001 office action, as well as the withdrawal of the other rejections and objections referenced in ¶ 4 of the current Office Action. The Examiner has maintained the rejections under part (B) and (C) of pages 5-7 of the July 5, 2001 office action.

The specification was amended to more accurately reflect this application's continuity information. No new subject matter was added by this amendment.

Applicant has cancelled claims 37 and 47 without prejudice and reserves the right to prosecute the subject matter of the cancelled claim in any future application claiming benefit or priority herefrom.

Claims 36, 39-40, and 43 have been amended to recite methods of treating, suppressing or altering the progression of cancer comprising administering to a patient anti-APRIL ligand antibodies, or pharmaceutical compositions thereof,

capable of interfering with an interaction between an APRIL ligand and its receptor. Claims 41-42 and 44-45 have been amended to recite methods for suppressing the growth of tumor cells comprising exposing the cells to antibodies directed to APRIL ligand polypeptides capable of interfering with an interaction between APRIL ligand and its receptor. Support for these claims may be found, for example, at page 8, lines 28-30; page 17, line 30 to page 19, line 28; and page 28, line 4 to page 29, line 32. The amendments do not add any new subject matter.

In sum, claims 36, 39-46, and 48-49 are pending.

THE REJECTIONS

Claims 36, 37, and 39-49 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.[2] The reasons for this rejection are described in parts (B) and (C) of pages 5-7 of the July 5, 2001 Office Action and on pages 2-3 of the instant Office Action. Applicant addresses each part of the rejection in turn, *infra*.

PART (B)

In part (B) of the July 5, 2001 office action, the Examiner has made the following allegations:

> 1. The specification fails to specifically teach a modified inhibitory form of APRIL effective for blocking the interaction between APRIL and its receptor. In the current Office Action, the

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[2] The rejection of claims 37 and 47 has been rendered moot because applicant has cancelled those claims herein.

Examiner alleged that newly added claims 47 and 43-45, drawn in part to an amino acid substitution analog of SEQ ID NO:2, are not described in the specification and that one of skill in the art cannot anticipate the amino acid sequence of said analog.

2. Claim 38, drawn to an anti-APRIL receptor antibody, is not supported by the specification because an APRIL receptor is not disclosed by the specification, and, even if one were disclosed, the art would not be able to anticipate what epitopes of the receptor would generate antibodies which would block the interaction between APRIL ligand and its receptor.

In response to the Examiner's rejection, applicant has amended claims 36, 39-40 and 43 herein to recite methods of treating, suppressing or altering the progression of cancer comprising administering to a patient *antibodies directed to APRIL ligand polypeptides*, or pharmaceutical compositions thereof. In response to the Examiner's rejection, applicant has amended claims 41-42 and 44-45 herein to recite methods for suppressing the growth of tumor cells comprising exposing said cells to *antibodies directed to APRIL ligand polypeptides*. Because amended claims 36 and 39-45 are no longer "drawn in part to amino acid substitution analog[s] of SEQ ID NO:2," applicant respectfully requests withdrawal of the rejection of these claims for the reasons stated in part (B) of the July 5, 2001 office action.

With respect to claims 46, 48 and 49, applicant traverses. These claims are drawn to methods for identifying agents capable of suppressing the growth of cell cultures that comprise cells that proliferate in response to the binding of a polypeptide encoded by SEQ ID NO:2 to its cell surface receptor. There is ample support in the specification for such methods.

For instance, the specification teaches that "[b]y making available purified and recombinant APRIL, the present invention provides assays which can be used to screen for drug candidates which are either agonists or antagonists of the normal cellular function, in this case, of APRIL or its receptor." *See* p. 26, lines 24-27. Example 2 provides specific examples of cell cultures that comprise cells that proliferate in response to the binding of a polypeptide encoded by SEQ ID NO:2 to its cell surface receptor. Specifically, addition of recombinant APRIL ligand enhanced proliferation of Jurkat T-lymphoma cell cultures. *See*, p. 33, lines 2-24. Similarly, cultures of NIH-3T3 cells transfected with APRIL ligand-encoding nucleic acids proliferated faster than control cultures. *See*, p. 23, lines 5-6. Thus, a person of skill in the art would recognize that he or she could use cells such as those described in Example 2 in the methods of claims 46, 48 and 49.

The methods recited in claims 46, 48 and 49 are analogous to the methods of screening hybridomas for specific monoclonal antibodies that were considered by the Federal Circuit in *In re Wands*. There, the Federal Circuit held that "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court further held that screening a large number of negative hybridomas did not render the claims non-enabled, stating that "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id.* at 1406. Similarly, practitioners in the field of cancer therapeutics discovery are prepared to screen large numbers of compounds to find those that have the desired effect on cultures of cancer cells.

In sum, amended claims 36 and 39-45, now drawn to antibodies directed to APRIL ligand polypeptides, are fully supported by the specification, which discloses expressed APRIL ligand polypeptides suitable for raising said antibodies. Claims 46 and 48-49, drawn to methods for identifying agents capable of suppressing the growth of cell cultures, are further supported by (1) the express teaching that these polypeptides can be used in assays to screen for drug candidates which are either agonists or antagonists of the normal cellular function of APRIL; and (2) the disclosure of cell cultures that are responsive to the expressed APRIL ligand polypeptides. Under *In re Wands*, applicant has provided an enabling disclosure for the pending claims and respectfully requests withdrawal of the rejections under these grounds.

PART (C)

In part (C) of the July 5, 2001 office action, the Examiner has made the following allegations:

> 1. For the reasons given in parts (A) and (B), the specification is not enabling for the disruption of the interaction between APRIL and the APRIL receptor.
>
> 2. The specification did not teach a specific antibody to APRIL or APRIL receptor that could prevent the binding of free APRIL to its receptor in a manner which would inhibit the growth of a malignant cell.
>
> 3. The examples of growth stimulation by APRIL ligand given in the specification all involve cells grown in suspension culture or cells grown in a monolayer. One cannot extrapolate results from such experimental systems to solid tumors *in situ* because of issues related to biological stability, half-

life, clearance from the blood, and target tissue penetration.[3]

The rejection of claims 36 and 39-45 based on the first allegation of part (C) has been rendered moot because the Examiner has withdrawn the rejection of the claims for the reasons stated in part (A) and because the rejection of these claims under part (B) have been obviated by their amendment herein, *supra*.

The rejection of claims 46 and 48-49 based on the first allegation of part (C), wherein said claims are drawn to methods for identifying agents capable of suppressing the growth of cell cultures, is traversed for the reasons discussed, *supra* at p. 7-9.

In response to the Examiner's rejection of claims 36 and 39-45 based on the second allegation of part (C), applicant traverses in part and states that these claims have been amended herein to recite antibodies directed to APRIL ligand polypeptides, or pharmaceutical compositions thereof, *supra*.

Amended claims 36 and 39-45, now drawn to an antibody directed to an APRIL ligand polypeptide capable of interfering with the interaction between an APRIL ligand and its receptor, are fully supported by the specification. The application provides nucleotide (SEQ ID NO:1) and amino acid (SEQ ID NO:2) sequences for APRIL ligands, as well as sequences that comprise soluble forms (page 17, lines 16-29).

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[3] In the current office action, the Examiner alleged that the application does not describe a single therapeutic method resulting in the reduction of tumor burden *in vivo* by the administration of the claimed antagonists. The Examiner also alleged that the specification does not provide a nexus between APRIL receptor antagonists and the treatment of cancer *in vivo*.

In other embodiments, the application discloses recombinant expression of APRIL ligand polypeptides (Example 2, page 32, line 23 to page 34, line 15), recombinantly expressed APRIL driving enhanced tumor cell proliferation (*id.*), and the generation of antibodies directed to the APRIL ligand polypeptides (page 17, line 30 to page 19, line 28).

Applicant submits herewith the Declaration of Paul D. Rennert, M.S. under 37 C.F.R. § 1.132. Mr. Rennert's Declaration provides evidence that the application enables a person of skill in the art to make antibodies directed to APRIL ligand polypeptides that interfere with the interaction between an APRIL ligand and its receptor, and that disrupting this interaction would reduce tumor cell proliferation.

In ¶ 5, Mr. Rennert declared that:

> "[a] person of skill in the art, having recombinant APRIL ligand polypeptides in hand, has the tools necessary to make antibodies directed to APRIL ligand polypeptides because methods for making antibodies were well known in the art by the time of the application's earliest filing date...A person of skill in the art, after making anti-APRIL ligand polypeptide antibodies, would then be able to screen different antibody preparations for those that interfere with the interaction between an APRIL ligand polypeptide and its receptor."

Thus, Mr. Rennert's Declaration provides compelling evidence that once a person of skill in the art has made anti-APRIL ligand polypeptide antibodies, it would be but routine experimentation to screen different antibody preparations for those that interfere with the interaction between an APRIL ligand polypeptide and its receptor. *See*, discussion of *In re. Wands*, *supra*.

In ¶ 6 of Mr. Rennert's Declaration, he described efforts in his laboratory that followed the teachings of the application that resulted in the generation of anti-APRIL ligand antibodies that block the interaction between APRIL

ligand and its receptor. In ¶ 8, Mr. Rennert declared that the specification would lead a person of skill in the art to believe that tumor cell proliferation may be reduced by providing an antibody that interferes with the interaction between APRIL and its receptor.

In sum, based on the express teachings of the application, the state of the art at the time of the earliest filing date of the application, and the evidence provided by Mr. Rennert in his Declaration, the application fully enables a person of skill in the art to make antibodies directed to APRIL ligand polypeptides that prevent the binding of an APRIL ligand polypeptide to its receptor and inhibit the growth of malignant cells. Therefore, applicant respectfully requests withdrawal of this rejection.

The rejection of claims 46 and 48-49 based on the second allegation of part (C), wherein said claims are drawn to methods for identifying agents capable of suppressing the growth of cell cultures, is traversed for the reasons discussed, *supra* at 7-9.

With respect to the third allegation in part (C), as discussed in the current Office Action, applicant traverses. Example 2 of the specification teaches that NIH-3T3 cells stably transfected with nucleic acids encoding an APRIL ligand polypeptide show an increase in cellular proliferation. Mice injected with these cells show a dramatically increased tumor burden when compared to mice injected with wild-type or mock-transfected NIH-3T3 cells.

In contrast to the Examiner's allegations, Mr. Rennert stated in ¶ 8 of his Declaration that the specification "provides a nexus between anti-APRIL ligand antibodies and the treatment of cancer *in vivo*." That nexus results from the disclosure in the application of (1) *in vitro* studies of cellular proliferation, (2) *in vivo* studies showing

APRIL ligand-driven increases in tumor burden, and (3) the ability to make an antibody directed to an APRIL ligand polypeptide capable of interfering with the interaction between an APRIL ligand and its receptor.

As evidence of this nexus, Mr. Rennert stated in ¶ 9 of his Declaration that he followed the teachings of the application and supervised experiments that showed that the anti-APRIL ligand antibodies that he described in ¶ 6 reduce tumor burden in mice injected with HT29 adenocarcinoma cells.

Mr. Rennert has concluded that this nexus "would lead a person of skill in the art to believe that tumor cell proliferation and tumor burden *in vivo* may be reduced by providing an antibody that interferes with the interaction between APRIL and its receptor." *Id.* at ¶ 8. Therefore, Mr. Rennert's declaration provides compelling evidence that the application enables methods of treating cancer *in vivo*.

The rejection of claims 46 and 48-49 based on the third allegation of part (C), wherein said claims are drawn to methods for identifying agents capable of suppressing the growth of cell cultures, is traversed for the reasons discussed *supra* at p. 7-9.

For the reasons stated, applicant has provided an enabling disclosure to support the pending claims and respectfully requests the withdrawal of the rejection under these grounds.

CONCLUSIONS

For the foregoing reasons, applicant believes the claims are in condition for allowance and respectfully

requests withdrawal of the remaining rejections.

Respectfully submitted,

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JUNE 13, 2002
Lillian Garcia

Signature of Person Signing

APPENDIX OF AMENDMENTS

In the specification

Please amend the paragraph on page 1 that spans lines 4-7 as follows:

This is a continuation-in-part of PCT/US98/19191, filed on September 11, 1998 [as a continuation of] which claims benefit from prior U.S. provisional application Serial No. 60/079,384 filed on March 26, 1998 [as a continuation in part of] and prior U.S. provisional application Serial No. 60/058,786 filed on September 12, 1997.

In the claims

36. (Amended) A method of treating, suppressing or altering the progression of a cancer comprising administering to a patient an effective amount of [a blocking agent] an antibody directed to an APRIL ligand polypeptide capable of interfering with an interaction between [April and its receptor capable of interfering with the association.] said APRIL ligand polypeptide and an APRIL receptor.

39. (Amended) The method of Claim 36, wherein [the blocking agent] said antibody is administered to [a] said patient in combination with [at least one] a chemotherapeutic agent.

40. (Amended) The method of [claim 39 further comprising the step of administering radiation therapy to said patient] claim 36, wherein said antibody is administered to said patient in combination with a radiation therapy.

41. (Twice Amended) A method of suppressing growth of a tumor cell that expresses an APRIL ligand polypeptide, comprising the step of [contacting] exposing said cell [with] to an effective amount of an agent [chosen] selected from the [list] group consisting of:

a. an antibody that binds specifically to said APRIL ligand polypeptide comprising at least about 102 amino acids or a soluble ligand polypeptide thereof;

b. an antibody that binds specifically to said APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 1-55 of SEQ ID NO:2, or a fragment thereof[, or a soluble ligand polypeptide thereof];

c. an antibody that binds specifically to said APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 157-250 of SEQ ID NO:2, a fragment thereof, or a soluble ligand polypeptide thereof;

d. an antibody that binds specifically to SEQ ID NO:2 or a soluble ligand polypeptide thereof; and

[e. an antibody that binds specifically to an amino acid substitution analog of SEQ ID NO:2 or a soluble ligand polypeptide thereof;

f. an antibody that blocks binding of said APRIL ligand polypeptide to an APRIL receptor polypeptide; and]

g.]e. an antibody that binds specifically to said APRIL ligand polypeptide and blocks [binding of] an interaction between said APRIL ligand polypeptide [to] and an APRIL receptor polypeptide.

42. (Twice Amended) A method of suppressing growth of a tumor cell that expresses an APRIL receptor polypeptide, comprising the step of [contacting] exposing said cell [with] to an effective amount of an agent [chosen] selected from the [list] group consisting of:

a. an antibody that binds specifically to an APRIL ligand polypeptide comprising at least about 102 amino acids or a soluble ligand polypeptide thereof;

b. an antibody that binds specifically to an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 1-55 of SEQ ID NO:2, or a fragment thereof[, or a soluble ligand polypeptide thereof];

c. an antibody that binds specifically to an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 157-250 of SEQ ID NO:2, a fragment thereof, or a soluble ligand polypeptide thereof;

d. an antibody that binds specifically to SEQ ID NO:2 or a soluble ligand polypeptide thereof; and

[e. an antibody that binds specifically to an amino acid substitution analog of SEQ ID NO:2 or a soluble ligand polypeptide thereof;

f. an antibody that blocks binding of an APRIL ligand polypeptide to said APRIL receptor polypeptide; and

g.]e. an antibody that binds specifically to an APRIL ligand polypeptide and blocks [binding of] an interaction between said APRIL ligand polypeptide [to] and said APRIL receptor polypeptide.

43. (Amended) A method for treating cancer comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a ligand selected from the group consisting of:] an antibody directed to an APRIL ligand polypeptide capable of interfering with an interaction between said APRIL ligand polypeptide and an APRIL receptor.

[1. an APRIL ligand polypeptide comprising at least about 102 amino acids;

2. an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 1 to 55 of SEQ ID NO:2, or a fragment thereof;

3. an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 157 to 250 of SEQ ID NO:2, or a fragment thereof; and

4. an APRIL ligand selected from:

(i) SEQ ID NO:2; or

(ii) an amino acid substitution analog of SEQ ID NO:2.]

44. (Amended) A method for suppressing growth of a tumor cell that expresses an APRIL ligand polypeptide, comprising the step of [contacting] exposing said cell [with] to an effective amount of [a ligand selected from the group consisting of:] an antibody directed to said APRIL ligand polypeptide capable of interfering with an interaction between said APRIL ligand polypeptide and an APRIL receptor.

[a) an APRIL ligand polypeptide comprising at least about 102 amino acids;

b) an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 1 to 55 of SEQ ID NO:2, or a fragment thereof;

c) an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 157 to 250 of SEQ ID NO:2, or a fragment thereof;

d) an APRIL ligand selected from:

(i) SEQ ID NO:2; or

(ii) an amino acid substitution analog of SEQ ID NO:2; and

e) a soluble APRIL ligand polypeptide comprising an N-terminal truncation from between amino acid numbers 81 to 139.]

45. (Amended) A method for suppressing growth of a tumor cell that expresses an APRIL receptor polypeptide, comprising the step of [contacting] exposing said cell [with] to an effective amount of [a ligand selected from the group consisting of:] an antibody directed to an APRIL ligand polypeptide capable of interfering with an interaction between said APRIL ligand polypeptide and said APRIL receptor polypeptide.

[a) an APRIL ligand polypeptide comprising at least about 102 amino acids;

b) an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 1 to 55 of SEQ ID NO:2, or a fragment thereof;

c) an APRIL ligand polypeptide comprising an amino acid sequence found in amino acids 157 to 250 of SEQ ID NO:2, or a fragment thereof;

d) an APRIL ligand selected from:

(i) SEQ ID NO:2; or

(ii) an amino acid substitution analog of SEQ ID NO:2; and

e) a soluble APRIL ligand polypeptide comprising an N-terminal truncation from between amino acid numbers 81 to 139.]